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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,529	08/04/1999	SUSAN MARY KINGSMAN	9192.9USWO	7151

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/28/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/254,529	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26-34,36-38 and 40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 26-34, 36-38, 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's arguments filed 03/13/03 have been fully considered but they are not found persuasive, for the reasons as set forth in the new grounds of rejections below:

Claims 25, 35 and 39 are canceled.
Claims 26-29, 31, 34 and 36-37 are amended.
Claims 24, 26-34, 36-38, 40-43 are pending and are examined in this office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR§1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim,* ***must include a complete listing of all claims*** *in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 24, 26-34, 36-38, 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description requirement**. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses a retroviral vector particle or a DNA construct, which when in the form of DNA provirus comprises i) a 5'LTR comprising a functional portion of HIV U3 and R region having Tat inducible activity, ii) any and all retroviral

polynucleotide response element (or retroviral response elements), which are responsive to a nucleus to cytoplasm transport factor, iii) a polynucleotides response element that is responsive to a functional equivalent of HIV Rev. iv) a functional equivalent of rev response element.

At best the specification as filed disclosed a retroviral particle and DNA construct which when in the form of DNA provirus comprises HIV 5'LTR that comprises HIV U3 and R regions having HIV Tat inducible activity. Furthermore the specification only disclosed a HIV Rev response element, which is responsive to HIV Rev. Besides the HIV LTR that comprises HIV U3 and R regions the specification as filed fail to disclose any functional portions thereof having Tat inducible promoter activity. Besides HIV Rev response element, which is responsive to HIV Rev protein the specification fails to disclose any other functional equivalent of Rev response element and functional equivalent of HIV Rev protein. In addition, it is unclear what is included or excluded in a retroviral particle that comprises all or a portion of any oncoretroviral genome. Limitations appearing in the specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Applicant is referred to the Interim guidelines on ***Written Description*** published December 21, 1999 in the Federal Register, Vol. 64, No. 244, pp. 71427-71440. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only disclosed HIV 5'LTR that comprises HIV U3 and R regions having HIV Tat inducible activity and HIV Rev response element (RRE) which is

responsive to HIV Rev protein but fails to disclose any and all functional and/or structural variants of HIV LTR U3 and R regions that are Tat inducible, HIV Rev response element and HIV Rev protein.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).*

In the instant case the variants (as claimed) has been defined only by a statement of function that broadly encompasses tat inducible activity or responsive to Rev which conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. Furthermore the variation as claimed also encompasses the conserved motifs, which are considered germane to the functional activity of HIV LTR, RRE and

Rev protein. The undefined variations as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). Furthermore method of using the vector particles or DNA construct also stand rejected, since the specification fails to disclose the retroviral particle and the DNA construct comprising the variants as claimed. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

2. Claims 24, 26-34, 36-38, 40-43 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for retroviral particle and DNA construct which when in the form of DNA provirus comprises HIV 5'LTR that comprises HIV U3 and R regions having HIV Tat inducible activity and comprises HIV RRE responsive to HIV Rev, does not reasonably provide enablement for retroviral particle and DNA construct which when in the form of DNA

provirus comprises any and all functional portions HIV LTR-U3R that has Tat inducible activity. In addition the specification does not reasonably provide enablement for any and all functional equivalent of HIV RRE, retroviral response element and HIV Rev protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims.

Nature Of Invention:

The invention relates to a Tat inducible retroviral vector particle.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses a retroviral vector particle or a DNA construct, which when in the form of DNA provirus comprises i) a 5'LTR comprising a functional portion of HIV U3 and R region having Tat inducible activity, ii) any and all retroviral polynucleotide response element or retroviral response element, which is responsive to a nucleus to cytoplasm transport factor, iii) a polynucleotides response element that is responsive to a functional equivalent of HIV Rev. iv) a functional equivalent of rev response element.

At best the specification as filed disclosed a retroviral particle and DNA construct which when in the form of DNA provirus comprises HIV 5'LTR that comprises HIV U3 and R regions having HIV Tat inducible activity. Furthermore the specification only disclosed a HIV Rev response element (a PRE or a retroviral response element), which is responsive to HIV Rev (a nucleus to cytoplasm transport factor). Besides the HIV LTR that comprises HIV 3 and R regions the specification as filed fails to disclose any functional portions thereof having Tat inducible promoter activity. Besides HIV Rev response element, which is responsive to HIV Rev

protein the specification fails to disclose any and all functional equivalent of Rev response element and functional equivalent of HIV Rev protein.

State Of Art And Predictability:

The art at the time of filing teaches that the mechanism by which HIV Tat induces HIV LTR is complex. HIV-1 Tat protein binds to a stem-loop structure at the 5' end of viral mRNA and relieves this inhibition by inducing a remodeling of the nucleosome arrangement downstream of the transcription-initiation site. Tat performs this activity by recruiting to the viral long terminal repeat (LTR) the transcriptional coactivator p300 and the closely related CREB-binding protein (CBP), having histone acetyltransferase (HAT) activity. Integrity of the basic domain of Tat is considered essential for this interaction (Marzio et al PNAS 95(23):13519-13524, 1998, see abstract). Even though a common mechanism of Tat transactivation through TAR is shared by HIV-1 and HIV-2 and SIV, the respective Tat gene products are not interchangeable in their effects (Brady et al PNAS, 91:365-369, 1994, see page 365, col.2). Furthermore, the Rev response element (RRE) is a 244-nt region in the env gene of HIV-1 that mediates transport of viral mRNA from the nucleus to the cytoplasm. Initially, the Rev protein binds with high affinity and specificity to a highly structured 30-residue region of the stem-loop IIB domain often termed the Rev binding element (RBE). See Huang et al PNAS USA. 97(10): 5107-5112, 2000, page 5107 col.1. In type D retroviruses, such as the simian retrovirus type 1 (SRV-1), genomic RNA is exported by cellular factor(s) that interact with a conserved cis-acting RNA element, the constitutive transport element (CTE) which is distinct from the REV-RRE system (Saavdra et al. Curr Biol. 7(9):619-28, 1997 page 619, Conclusion). Besides REV-RRE system the applicant fails to disclose any polynucleotides response element or retroviral response

element that is responsive to a nucleus to cytoplasm transport factor. In addition, it is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). Furthermore it is unclear how one skill in the art would identify and use a functional equivalent of HIV Rev that would bind to a functional equivalent of Rev response element in this case. The invention as claimed encompasses structural and/or functional variations in both RRE and Rev components, wherein function of one is defined as function of other. In addition it is unclear how one skill in the art would use the retroviral particles and DNA construct to transduce any target cell, since the applicant fails to disclose the claimed variants required to make the DNA construct and/or retroviral particles. Therefore, considering the state of the art at the time of filing the applicant has not presented enablement commensurate in scope with the claims.

Quantity Of Experimentation Required:

Considering the state of the art at the time of filing making any and all Tat inducible promoters, variants of RRE or Rev that have REV/RRE-like functional activity is not considered routine in the art and without sufficient guidance to a specific variants (as claimed) the

experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3 1and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

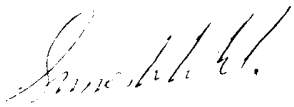
Claim 31 recites the limitation "the retroviral response element comprises all or portion of a lentiviral response element" in line 1-2. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



SUMESH KAUSHAL
PATENT EXAMINER